

**Amendments to the Specification:**

Please amend the specification as follows:

Please replace the paragraph starting at page 14, line 18, with the following rewritten paragraph:

The following figures elucidate the invention: Figure 1 shows the result of the MPSS experiment on the comparison of the left (ischemic; y-axis) to the right (non-ischemic; x-axis) hemisphere. Given are the frequency of occurrences of the signatures identified. A signature for TWEAK ("GATCCCTGTGGATTGT") (**SEQ ID NO: 5**) was identified at a frequency of 41 in the ischemic hemisphere and 0 in the contralateral, non-ischemic hemisphere (arrow;  $p = 1.12 \times 10^{-12}$ ).

Please replace the paragraph starting at page 16, line 6 with the following rewritten paragraph:

To prepare cDNA-libraries for the MPSS analysis, 5  $\mu$ g of total RNA was denatured at 70 °C with 50 pmol of T7-tagged-BsmBI-oligo-dT18V primer (GGC CAG TGA ATT GTA ATA CGA CTC ACT ATA GGG CTG CAT TGA GAC GAT TCT TTT TTT TTT TTT TTT TTV) (**SEQ ID NO: 7**), cooled on ice, reverse, transcribed with 200 U of Superscript II at 42 °C for 1 h in 1 reaction buffer, 10 mM dithiothreitol (all reagents Invitrogen, Karlsruhe, Germany) and 0.5 mM each dNTP (Roche Diagnostics, Mannheim, Germany) in 25  $\mu$ L. Second strand cDNA synthesis was performed by adding 40 U of DNA polymerase I, 2 U of RNase H, 10 U Escherichia coli DNA ligase and 0.5 mM each dNTP in 1 second-strand buffer (Invitrogen) in a final volume of 100  $\mu$ L for 2 h at 16 °C. RNA was hydrolyzed in the presence of 100 mM NaOH at 65 °C for 20 min. The reaction product was phenol : chloroform purified and precipitated with ammonium-acetate in the presence of PelletPaint (Calbiochem-Novabiochem, Bad Soden, Germany).

Please replace the paragraph starting at page 16, line 23 with the following rewritten paragraph:

The aRNA was purified using RNeasy columns (Qiagen, Hilden, Germany) and quantified. For each sample, 8 µg of aRNA was reverse transcribed in the presence of 1 µg random hexamer primer under the same conditions as for the first synthesis (see above). Second-strand strand synthesis was performed as a linear PCR with a 5'-biotin tagged BsmBI oligo-dT18 primer (biotin-GACATGCTGCATTGAGACGATTCTTTTTTTTTTT) (**SEQ ID NO: 9**) and AdvantageTaq 2 (Clontech GmbH ; Heidelberg, Germany) according to the manufacturer's instructions.

Please replace the paragraph starting at page 17, line 17 with the following rewritten paragraph:

RNA was isolated according to standard protocols (Chomczynski and Sacchi (1987), *Anal. Biochem.*, 162,156-159), followed by Qiagen RNeasy mini kit purification. Tissue samples were taken from mouse ipsi-and contralateral to the lesion side 20h after MCAO. cDNA was synthesized from 10 µg total RNA using oligodT primers, superscript II reverse transcriptase (Gibco) using standard conditions. Quantitative PCR was performed using the Lightcycler® system (Roche Diagnostics, Mannheim, Germany) with SYBR-green staining of DNA doublestrands. Cycling conditions were as follows : 10 min 95°C, 5 sec 95°C, 10 sec 65°C, 30 sec 72°C ; 10 sec 87°C for 50 cycles. Melting curves were done with the following parameters: 95°C cooling to 50°C ; ramping to 99°C at 0.2°C/sec. The following primer pairs were used :"mm tweak-144s" AAC GCT GTC TGC CCA GGA GCC (**SEQ ID NO: 10**) and "mm tweak-305as" GGC CGA GGA TGA ACC TCA TAA TGG (**SEQ ID NO: 11**). The Lightcycler PCR was performed using the SYBR green master mix, following the manufacturer's recommendations (Roche Diagnostics). Specificity of products was ensured by melting point analysis and agarose gel electrophoresis. cDNA content of samples was normalized to the expression level of Cyclophilin (primers :"cyc5" ACC CCA CCG TGT TCT TCG AC (**SEQ ID NO: 12**); "acyc300" CATTGCCATGGACAAGATG (**SEQ ID NO: 13**)). Relative regulation levels were derived after normalization to cyclophilin, and comparison to the sham-operated animal. Error bars indicate standard deviations, these are calculated from 3- fold serially diluted cDNA-samples, and reflect reliability of measurements.

Please replace the paragraph starting at page 19, line 4 with the following rewritten paragraph:

In order to monitor the effect of TWEAK activation in cell culture, primary neuronal cultures (or other neural cells) can be assayed for cell death promoting activities of TWEAK, and the TWEAK receptor Fn14. Primary neuronal cultures: Ten to 12 cortices or hippocampi are dissected from rat embryos E18. The tissue is dissociated using 10 mg/ml trypsin, 5 mg/ml EDTA/DNase (Roche diagnostics, Mannheim, Germany) in HBSS (BioWhitakker, Taufkirchen, Germany). The digestion is stopped using four parts neurobasal medium containing 1X B-27 supplement (Invitrogen, Karlsruhe, Germany), 0.5 mM L-glutamine, and 25  $\mu$ M glutamate. After centrifugation, the pellet is dissolved in 5 ml medium and cells are plated at a density of 250,000 cells per well of a 24-well-plate on glass cover slips coated with poly-L-lysine. For treatment with the NO-donor NOR3 (Sigma), neurons are treated after 21 days in culture with increasing concentrations of NOR-3 for 24 h. TWEAK can then be added in increasing concentrations. Also, antagonists of TWEAK or the TWEAK receptor can be added. As read-outs for neuronal cell death, various methods can be used. For example, PARP cleavage can be assayed using Western blots. Western blots for PARP cleavage: Primary neurons are scraped off the plate and washed twice in ice-cold PBS containing 2.5 mg/ml pepstatin (Sigma- Aldrich, Seelze, Germany) und aprotinin (1: 1000, Sigma-Aldrich). Pellets are resuspended in 1 volume 2% SDS (40  $\mu$ l), and 5  $\mu$ l benzonase solution (40  $\mu$ l 100 mM MgCl<sub>2</sub> and 9  $\mu$ l benzonase, Roche Diagnostics, Mannheim, Germany) is added. After solubilization, 1 volume PBS is added and the protein concentration determined (BCA-Test, Pierce, Rockford, IL, USA). After denaturing at 95°C for 5 min, 100 ug is run on 8% SDS-polyacrylamide gels. Proteins are transferred to nitrocellulose membranes (Protan BA79, Schleicher & Schuell, Dassel, Germany) using a semi-dry-blotting chamber (Whatman Biometra, Göttingen, Germany). Blots are blocked with 5% milk powder in PBS/0. 02% Tween 20, washed three times with PBS/0.02% Tween 20, and incubated for 1 h at room temperature with the primary antibody (anti-cleaved-PARP-antibody, Cell Signalling, 1: 1000). After washing, the blots are incubated with the secondary antibody (anti-rabbit-antiserum HRP-coupled or anti-mouse-antiserum HRP-coupled, Dianova, Hamburg, Germany 1: 4000) for 1 h at room temperature. Signals are detected using the supersignal

chemiluminescence system (Pierce, Rockford, USA) and exposed to **Hyperfilm-ECL** **HYPERFILM-ECL** (Amersham Pharmacia Biotech, Piscataway, NJ, USA). PARP cleavage can be quantified on scanned autoradiographs using Windows ImageJ v1. 29 (<http://rsb.info.nih.gov/ij/index.html>). located on the world wide web at //rsb.info. nih.gov/ij/index.html).

Please replace the paragraph starting at page 20, line 1 with the following rewritten paragraph:

Alternatively, the **cell-death ELISA (Roche diagnostics)** **CELL DEATH DETECTION ELISA** (Roche Diagnostics GmbH, Mannheim, Germany), LDH assay, the **caspase-glo assay** **CASPASE GLO ASSAY** (Promega), or any other assay used to determine cell death or cell survival can be used that is known to a person skilled in the art.